

Original



Impaired β-cell function and decreased insulin sensitivity in subjects with normal oral glucose tolerance but isolated high glycosylated hemoglobin

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Abstract. The pathophysiology is distinct in various state of glucose metabolism abnormalities. As the defect of individuals with normal oral glucose tolerance (NGT) but isolated high glycosylated hemoglobin (HbA1c), *i.e.* iHH, was ambiguous, we aimed to investigate the insulin sensitivity and β -cell function of iHH. According to the ADA criteria of HbA1c cut-off point (5.7%), 3,517 subjects with NGT screened from a total of 7,855 middle-aged and elderly Chinese without known diabetes were divided into two groups, 1,877 subjects with HbA1c < 5.7% and 1,640 with HbA1c \geq 5.7% (*i.e.* iHH). A variety of indexes from blood glucose and insulin levels of oral glucose tolerance were calculated to evaluate insulin sensitivity and β -cell function. Compared with subjects with HbA1c < 5.7%, individuals with iHH had increased homeostasis model assessment of insulin resistance (HOMA-IR), early-phase and total insulin release indexes (insulin release index 30 min and 120 min, *i.e.* INRS30 and INSR120), and decreased Matsuda insulin sensitivity index (Matsuda ISI) and early-phase disposition index (DI30). After adjustment for confounding factors, the significant difference of HOMA-IR and INSR30 between the two groups vanished, however, Matsuda ISI and DI30 remained significantly lower and INSR120 was still higher in iHH group compared with HbA1c < 5.7%. In conculsion, subjects with NGT may not be perfectly healthy in glycometabolism, those with iHH have impaired early-phase β -cell function and decreased insulin sensitivity.

Key words: Glycosylated hemoglobin, β-cell function, Insulin resistance, Oral glucose tolerance

THE AMERICAN DIABETES ASSOCIATION (ADA) has proposed adoption of glycated hemoglobin (HbA1c) for diagnosis of pre-diabetes and overt diabetes [1]. The World Health Organization (WHO) has also advocated a similar HbA1c cutoff for the diabetes diagnosis [2]. A lot of studies have compared the diagnostic performance of HbA1c with fasting plasma glucose (FPG) and 2 hour-plasma glucose (2h-PG) of oral glucose tolerance test (OGTT) in various populations [3-7]. Using OGTT as gold standard, most studies demonstrated that HbA1c had poor sensitivity for diagnosis of prediabetes and diabetes. There was great discordance between HbA1c and blood glucose in the diagnosis of diabetes. Therefore, there are a large proportion of peo-

ple having normal glucose tolerance (NGT) but high HbA1c, which could be defined as isolated high HbA1c (abbreviated to iHH in this article).

Previous studies have shown that there was distinct defect in pathophysiology of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). IFG have marked increased hepatic insulin resistance, and impaired first-phase insulin secretion. Whereas, IGT was markedly decreased in insulin sensitivity of skeletal muscle, and both the first- and second-phase insulin secretion was decreased [8-10]. Accordingly, we speculated that iHH discordant with blood glucose criteria may indicate different pathogenetic mechanisms of dysglycemia. However, until now few studies focused on individuals with iHH. So, the aim of our study was to investigate the insulin sensitivity and β -cell function of iHH, which may reveal the underling pathophysiologic mechanism.

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Materials and Methods

Subjects

The present work was one part of the baseline survey from Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study, which was conducted among 259,657 adults, aged 40 years and older in 25 communities across mainland China, from 2011 to 2012 [11-14]. The subjects of the present study came from the survey of urban population who lived in Gulou district, Nanjing city, China. People older than 40 years were invited to participate in this study through advertising within local clinics and in posters. A total of 10,027 participants older than 40 years were recruited from June to December 2011 (Shown in Fig. 1). After excluding 1,758 subjects who had been diagnosed as diabetes previously, 227 did not complete questionnaire, and 187 did not complete oral glucose tolerance test (OGTT), 7,855 subjects were available for analysis. Of these 7,855 individuals, 3,517, 2,350 and 865 subjects were identified as NGT, IFG/IGT (5.6 mmol/L \leq FPG <7.0 mmol/L and/or 7.8 mmol/L \leq 2h-PG < 11.1 mmol/L), and newly diagnosed diabetes (NDM, FPG \geq 7.0 mmol/L and/or $2h-PG \ge 11.1 \text{ mmol/L}$) respectively. Thus, these 3,517 NGT subjects were selected for current analysis of our study. According to the criteria of ADA with HbA1c cut-off point at 5.7%, the NGT cohort were divided into two groups, 1,877 subjects with HbA1c < 5.7% and 1,640 with HbA1c \geq 5.7% (*i.e.* iHH, which included HbA1c = 5.7–6.4% and \geq 6.5%). Additionally, among IFG/IGT subjects, those with 5.6 mmol/L \leq FPG < 7.0 mmol/L but 2h-PG < 7.8 mmol/L were defined as isolated impaired fasting glucose (iIFG, n = 1,461), and those with 7.8 mmol/L \leq 2h-PG < 11.1 mmol/L but FPG < 5.6 mmol/L were called isolated impaired glucose tolerance (iIGT, n = 897).

Measurements and data collection

Every participant was interviewed by trained doctors or nurses and completed a questionnaire covering medical history, physical activity, alcohol intake and smoking habits. If one of parents or siblings had been diagnosed with diabetes, participant was defined as having family history of diabetes mellitus (FHDM). Smoking status included non-smokers, ex-smokers, and current smokers if individuals smoked daily for at least 12 months regardless of the amount and type of smoking. Alcohol consumption was divided into 3 categories: abstinent (<20.0 g/wk), mild to moderate (20.0–199.9 g/wk), and heavy (≥200 g/wk). Physical activity level was classified as



Fig. 1 Flow diagram of recruitment of participants available for analysis

low, moderate, or high based on the International Physical Activity Questionnaire (IPAQ) [15].

Anthropometric measurements including height, weight, waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse were performed by professional physicians. Body mass index (BMI) was calculated by dividing weight in kilograms (kg) by height in squared meter (m²). Blood pressure and pulse were taken as the mean of 3 consecutive measurements after at least 5 minutes of rest.

After 12-hour fasting, morning blood samples were obtained from an antecubital vein for FPG (i.e. G0), fasting serum insulin (INS0), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglyceride (TG). Then the 75-g oral glucose tolerance tests (OGTT) were performed, and venous blood samples were obtained at 30 and 120 minutes after glucose load for measuring the plasma glucose (30min plasma glucose G30, and 120min plasma glucose G120, i.e. 2h-PG), serum insulin (30min serum insulin INS30, and 120min serum insulin INS120). HbA1c was examined with capillary blood (Variant II, Bio-Rad). Serum insulin was measured by radioimmunoassay (Iodine ^{[125}I] Insulin Radioimmunoassay Kit, Beijing North Institute of Biological Technology). Plasma glucose was measured by hexokinase method (AU5400, Olympus). HDL, LDL, and TG were measured using chemiluminescence methods on the auto-analyzer (Modular E170, Roche).

Calculations

Insulin resistance was estimated using the homeostasis model assessment (HOMA-IR), which was calculated as follows: insulin (mIU/L) × glucose (mmol/L)/22.5 [16]. Matsuda insulin sensitivity index (Matsuda ISI) was used to evaluate whole-body insulin sensitivity, which was calculated as $10,000/\sqrt{(G0 \times INS0) \times (\overline{G} \times \overline{INS})}$, where \overline{G} and \overline{INS} are the average levels of plasma glucose in mg/dL and insulin in mIU/L of OGTT, respectively [17].

The early-phase insulin release was calculated as the ratio of the insulin area under curve (AUC) to glucose AUC from 0 to 30 min (InsAUC30/GluAUC30), which is defined as INSR30. InsAUC120/GluAUC120 (insulin release index 120, INSR120) is a surrogate index for total insulin release, where InsAUC120 and GluAUC120 are the area under insulin (mIU/L) and glucose (mmol/L) curves during 0 to 120 min of the OGTT [18]. Two disposition indexes (DI) were calculated based on the product of insulin sensitivity × insulin release. DI30 (INSR30)

× Matsuda ISI) and DI120 (INSR120 × Matsuda ISI) were used to assess ability of early-phase and total β -cell response to insulin sensitivity respectively [19].

Statistical analyses

All statistical analyses were carried out using the Statistical Package for Social Science for Windows (SPSS, Version 13.0). Student's t test was used to analyze group differences. Analysis of covariance was used to adjust confounding factors. Multivariable stepwise logistic regression was used to study the association of HbA1c categories with insulin sensitivity and β -cell function.

Results

Among the total 7,855 available participants, the respective prevalence of pre-diabetes (IFG/IGT) and newly diagnosed diabetes by OGTT criteria was 44.2% and 11.0%. The 3,517 subjects with NGT had average HbA1c of $5.61 \pm 0.37\%$ (range 3.4-8.1%) and BMI of $23.48 \pm 2.96 \text{ kg/m}^2$ (range 14.73–44.63 kg/m²), with mean age of 54.57 ± 9.14 years (range 40–79 years). Among these NGT subjects, the percentage of HbA1c < 5.7%, 5.7-6.4% (pre-diabetes by ADA criteria), and \geq 6.5% (NDM by ADA criteria) were 53.4%, 46.6% and 1.4%, respectively. Table 1 showed the characteristics of two groups divided by the cut-off point of HbA1c = 5.7%. Sex distributions, SBP, smoking, drinking, and physical activity were not different between the two group. Subjects with HbA1c \geq 5.7%, *i.e.* iHH had higher age, BMI, WC, TG, LDL and lower HDL. Fig. 2 showed the plasma glucose and serum insulin levels of OGTT, iHH subjects had significantly higher glucose and insulin levels than those with HbA1c < 5.7% at 0, 30, and 120 min during OGTT.

Insulin concentration curves during OGTT were analyzed and divided into two patterns: pattern 1, insulin level peaked at 30 min during OGTT and decreased at 120 min, (N = 2,458, 69.9% of total NGT subjects); pattern 2, insulin level increased continually from 0 min to 120 min and peaked at 120 min (N = 1,059, 30.1% of total NGT subjects) (Fig. 3). The proportion of different insulin secretion curves in subjects with iHH and HbA1c < 5.7% was significantly different (Table 2). More proportion of iHH subjects had pattern 2 compared with HbA1c < 5.7% subjects (32.7% vs. 27.8%, p < 0.05).

Fig. 4 demonstrated insulin sensitivity and β -cell function of subjects with different HbA1c and glucose tolerance. In subjects with iHH, the insulin resistance index

	HbA1c < 5.7	$HbA1c \ge 5.7$	<i>p</i> value
NO.	1,877	1,640	
Age (years)	52.95 ± 9.09	56.41 ± 8.85	< 0.001
Sex (male/female)	532/1,345	459/1,181	0.815
Body mass index (kg/m ²)	23.34 ± 2.98	23.63 ± 2.94	0.004
Waist circumference (cm)	80.52 ± 8.66	81.68 ± 9.31	< 0.001
Systolic blood pressure (mmHg)	122.97 ± 15.97	123.33 ± 16.00	0.503
Diastolic blood pressure (mmHg)	76.04 ± 10.28	75.04 ± 10.02	0.004
Triglyceride (mmHg)	1.27 ± 0.87	1.38 ± 0.88	< 0.001
High density lipoprotein cholesterol (mmol/L)	1.39 ± 0.34	1.33 ± 0.34	< 0.001
Low density lipoprotein cholesterol (mmol/L)	2.70 ± 0.72	2.83 ± 0.76	< 0.001
HbA1c (%)	5.34 ± 0.25	5.92 ± 0.23	< 0.001
Family history of diabetes (Yes/No)	224/1,653	245/1,395	0.009
Smoking (non-/ex-/current smoker)	1,530/73/301	1,343/60/237	0.383
Drinking (abstinent/mild to moderate/heavy)	1,320/429/128	1,152/381/107	0.919
Physical activity (low/moderate/high)	940/580/357	798/543/299	0.370

 Table 1
 Characteristics of 3,517 participants with NGT subdivided by HbA1c level

Data were expressed as means \pm SD. Differences between the group of HbA1c < 5.7 and HbA1c \geq 5.7 were estimated using unpaired Student's *t*-test (or chi-square test for classified data). Abnormally distributed continuous variables (triglyceride) were log-transformed before analysis, non-transformed values displayed for ease of interpretation.



Fig. 2 The plasma glucose and serum insulin levels during OGTT of 3,517 subjects with normal glucose tolerance grouped by HbA1c cut-off point 5.7% Values were expressed as means ± SD.

(HOMA-IR) was higher compared with those with NGT and HbA1c < 5.7% (2.69 \pm 1.70 vs. 2.54 \pm 1.59, p =0.004). However, the difference was not significant. Compared with NGT and HbA1c < 5.7% subjects, the insulin sensitivity marker (Matsuda ISI) of iHH was significantly decreased (5.22 \pm 2.89 vs. 5.75 \pm 3.05, p <0.001). After adjustment for confounding factors, the difference was significant. Interestingly, iHH subjects presented higher early-phase and total insulin release levels (INSR30 6.36 \pm 4.23 vs. 6.06 \pm 4.01, p < 0.001; INSR120 8.40 \pm 5.16 vs. 7.73 \pm 4.80, p < 0.001). Further adjustment for confounding factors invalidated the difference of early-phase insulin release, but the total insulin release remained statistically significant. The earlyphase β -cell response to insulin sensitivity (DI30) of iHH subjects remarkably decreased compared with NGT and HbA1c < 5.7% subjects regardless of the influence of confounding factors. Furthermore, the total β -cell



Two patterns of insulin concentration curves during OGTT Fig. 3 Values were expressed as means \pm SD.

Table 2 The proportion of different insulin secretion curves in subjects with HbA1c < 5.7% and HbA1c ≥ 5.7

	Pattern 1	Pattern 2	Proportion of Pattern 2	<i>p</i> value
HbA1c < 5.7	1,355	522	27.8%	< 0.05
$HbA1c \ge 5.7$	1,103	537	32.7%	

response to insulin sensitivity (DI120) was not different between the two HbA1c categories before or after adjustment for covariates.

We also compared insulin sensitivity and β -cell function of iHH with iIFG and iIGT subjects (shown in Fig. 4). Although both iIFG and iIGT subjects had significantly increased insulin resistance (HOMA-IR) and decreased insulin sensitivity (Matsuda ISI), these two groups had marked difference (Fig. 4A and D). iIFG subjects had higher HOMA-IR (p < 0.05), on the other hand, iIGT subjects showed more sever decrease of Matsuda ISI (p < 0.001). The early-phase insulin release (INSR30) decreased in both iIFG and iIGT group, however, the total insulin release (INSR120) compensatorily increased in iIGT group (p < 0.05) but not in iIFG group (Fig. 4B and E). The early-phase and total disposition index (DI30 and DI120) were reduced significantly in both iIFG and iIGT group. Meanwhile, lower DI30 and DI120 were observed in iIGT subjects compared with iIFG ones (Fig. 4C and F). Interestingly, compared with iFG and iIGT group, the increase of HOMA-IR and decrease of Matsuda ISI of iHH group was lesser. In contrast, the decrease of early-phase DI30 in iHH group was equivalent to iIFG group but lesser than iIGT. In addition, the compensatory increase of total insulin release index (INSR120) in iHH group was comparable with iIGT.



To further explore the relationship between HbA1c categories and insulin sensitivity and β -cell function, we defined the insulin resistance by HOMA-IR > 4th quartile (IR-HOMA-IR) or Matsuda ISI < 1st quartile (IR-Matsuda ISI), and impaired β -cell response to insulin sensitivity by DI30 (IB-DI30) or DI120 (IB-DI120) < 1st quartile of subjects with absolute normal OGTT and HbA1c (i.e. NGT and HbA1c < 5.7%). In logistic regression analysis (showed in Table 3), individuals with iHH showed greater chance to have insulin resistance defined by Matsuda ISI (IR-Matsuda ISI, OR = 1.460 [95% CI 1.252-1.701], p < 0.001) but not HOMA-IR. After adjustment for age, FHDM, BMI, WC, lipid profiles and FPG, the OR of IR-Matsuda ISI persisted significantly (OR = 1.329 [95% CI 1.119 - 1.573], p < 0.001). Further adjustment for age, FHDM, BMI, WC, lipid profiles, 2h-PG weaken the OR (OR = 1.275 [95% CI 1.113-1.539], p = 0.003), but the OR remained significantly. Our study also showed that iHH subjects had higher risk of early phase β -cell response to insulin sensitivity (IB-DI30, OR = 1.316 [1.129 - 1.533], p < 0.001), the OR was still significant after adjustment for confounding factors including FPG (OR = 1.272 [95% CI 1.103–1.439], p = 0.016) and 2h-PG (OR = 1.182 [95% CI 1.095–1.399], p = 0.035). There was no significant association was observed between HbA1c categories and risk of impaired total phase β -cell response to insulin sensitivity (IB-DI120). iHH was also associated with higher risk of metabolic syndrome by IDF criteria (MS-IDF, OR = 1.295, 95% CI [1.076–1.558], p = 0.006), but the association was attenuated after adjustment for sex, age, family history of diabetes.

Discussions

Since the newly diagnostic criteria of HbA1c proposed



Fig. 4 Comparison of insulin sensitivity and β-cell function of subjects grouped by HbA1c and glucose tolerance NGT&HbA1c < 5.7%: subjects with FPG < 5.6 mmol/L, 2h-PG < 7.8 mmol/L and HbA1c < 5.7%; iHH: subjects with FPG < 5.6 mmol/L, 2h-PG < 7.8 mmol/L but HbA1c ≥ 5.7%; iIFG: subjects with 5.6 mmol/L ≤ FPG < 7.0 mmol/L and 2h-PG < 7.8 mmol/L; iIGT: subjects with 7.8 mmol/L ≤ 2h-PG < 11.1 mmol/L and FPG < 5.6 mmol/L.</p>

* p < 0.05, *** p < 0.01, compared with NGT&HbA1c < 5.7% group. [§] p < 0.05, difference between iHH and iIFG group. [§] p < 0.05, ^{§§} p < 0.01, ^{§§§} p < 0.001, difference between iIFG and iIGT group. [#] p < 0.05, ^{##} p < 0.01, ^{###} p < 0.001, difference between iHH and iIGT group. NS, no significance. All differences were adjusted for age, body mass index, waist circumference, diastolic blood pressure, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol, fasting plasma glucose and family history of diabetes. Values were expressed as means ± SD.

Table 3 Association of HbA1c categories with insulin resistance, impaired β -cell function and metabolic syndrome

	OR1	<i>p</i> 1	OR2	<i>p</i> 2	OR3	р3
IR-HOMA-IR	1.123 (0.964–1.309)	0.136	1.039 (0.891–1.228)	0.629	1.026 (0.877–1.196)	0.668
IR-Matsuda ISI	1.460 (1.252–1.701)	< 0.001	1.329 (1.119–1.573)	< 0.001	1.275 (1.113–1.539)	0.003
IB-DI30	1.316 (1.129–1.533)	< 0.001	1.272 (1.103–1.439)	0.016	1.182 (1.095–1.399)	0.035
IB-DI120	1.137 (0.976–1.325)	0.099	1.006 (0.927–1.197)	0.277	1.005 (0.915–1.191)	0.297
MS-IDF	1.295 (1.076–1.558)	0.006	0.979 (0.764–1.253)#	0.864#	—	—

IR-HOMA-IR: insulin resistance defined by HOMA-IR; IR-Matsuda ISI: insulin resistance defined by Matsuda ISI; IB-DI30: impaired β cell function defined by DI120; MS-IDF: metabolic syndrome according to IDF criteria. OR: odds ratio of subjects with iHH having insulin resistance or impaired β cell function compared with those with HbA1c < 5.7. OR1: Not adjusted for any confounding factors. OR2: Adjusted for age, body mass index, waist circumference, diastolic blood pressure, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol, fasting plasma glucose and family history of diabetes (*: adjusted for sex, age, family history of diabetes). OR3: Adjusted for age, body mass index, waist circumference, diastolic blood pressure, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol, 2 hour-plasma glucose and family history of diabetes.

by International Expert Committee and affirmed by the ADA [1, 20], substantial epidemiological studies had compared the capability of HbA1c and OGTT to diagnose diabetes and detect individuals at high risk of developing diabetes. As the majority of these studies reported, the use of HbA1c criteria resulted in excessive NGT and missed a large proportion of high-risk and diabetes. In the Insulin Resistance Atherosclerosis Study (IRAS), HbA1c 5.7-6.4% only detected 23.6% individuals at-risk of diabetes, and HbA1c $\geq 6.5\%$ only detected one-third individuals diagnosed as diabetes by the 1999 WHO criteria [3, 4]. The diagnostic criterion of HbA1c identified diabetes with sensitivity and specificity 38.7 and 99.6%, respectively in the Telde Study of Spain [5]. In a combined three datasets of Non-Hispanic white and black, with the ADA criteria of 5.7-6.4% for pre-diabetes, and HbA1c 6.5% for diabetes, HbA1c merely correctly identified 30% individuals with diabetes, 29% with prediabetes, and 35% with dysglycemia (including prediabetes and NDM) [6]. At HbA1c cutoff point of 6.5%, the sensitivity for newly diagnosed diabetes was <30% in a Chinese cohort of Qingdao [7]. Our data was in agreement with those observations. In our study, when the HbA1c cutoff point of 6.5% was used to identify newly diagnosed diabetes, the sensitivity and specificity were 53.1 and 96.4%, respectively. Compared with FPG and 2h-PG, the HbA1c cutoff point of 5.7% is seemingly less sensitive to identify individuals at risk for diabetes, and the concordance rate of HbA1c and OGTT for identifying dysglycemia was only 53.5% in our study.

However, the low concordance of HbA1c with FPG and 2h-PG does not mean it is a dispensable assay for diagnosing diabetes or for identifying individuals at high risk. The disconcordance may show the different pathophysiologic processes detected by HbA1c and OGTT. HbA1c is used as a marker of average blood glucose levels over a 2 to 3 month period of time, which reflects the combination of long-term exposure to basal and postprandial hyperglycemia. Conversely, FPG and 2h-PG were just instant blood glucose. Besides, the reproducibility of OGTT was poor, and variance of living environment such as sleep, diet and exercise, can significantly affect the results of glucose tolerance, this might be one of the reason why high HbA1c independently reflected impaired glucose metabolism.

More importantly, HbA1c, FPG, and 2h-PG may assess different aspects of glucose metabolism. A study in 6,414 Finnish men showed defects of peripheral insulin sensitivity started within normoglycemic range [18]. Consistent with this study, our data demonstrated that people with normal glucose tolerance and iHH had decreased Matsuda ISI which represents impairment of peripheral insulin sensitivity. IFG and IGT are widely thought as two major kinds of prediabetic glycometabolism, and the pathophysiologic abnormalities of insulin sensitivity and β -cell function in these two states are distinct [21]. Individuals with IFG have more severe insulin resistance in liver than in skeletal muscle. In contrast, insulin resistance in subjects with IGT is more serious in skeletal muscle than in liver [8, 9]. Both IFG and IGT manifest impaired first phase insulin secretion, whereas decreased second-phase insulin secretion was only detected in subjects with IGT [10]. The results of our data which were consistent with this standpoint. In the present study, subjects with iIFG had higher HOMA-IR which is the marker of liver insulin resistance, and iIGT subjects had more sever decrease of Matsuda ISI which mainly reflects peripheral insulin sensitivity. The early-phase DI30 and total disposition index DI120 decreased more seriously in iIGT group than iIFG.

A study in Mexican American subjects demonstrated that compared with subjects with NGT and HbA1c < 5.7%, subjects with NGT and HbA1c = 5.7-6.4% had comparable β-cell function, however, subjects with IFG and/or IGT and HbA1c = 5.7-6.4% had marked decreased β -cell function [22]. Nonetheless, another two studies in Asian population reported that increased HbA1c levels were associated with impaired insulin secretion rather than insulin resistance [23, 24]. These above studies were not specific to iHH, subjects participated in these studies included NGT, IFG, IGT and even NDM. In the present study, individuals with iHH had increased indices of insulin resistance, especially peripheral insulin resistance. Although the insulin release indexes IN120 were higher in iHH subjects, the earlyphase insulin release response to insulin resistance DI30, as an indicator of β -cell function adjustment for insulin resistance, decreased significantly in subjects of iHH. Similarly, in a study of overweight/obese adolescents, subjects with HbA1c 5.7 to <6.5% had significantly lower insulin sensitivity and β -cell function versus those with normal HbA1c [25]. Previous studies had demonstrated that impairment of insulin secretion and insulin sensitivity starts from the NGT range of 2-h plasma glucose, and minimally elevated glucose may indicate the onset of insulin sensitivity and β-cell function impairment [26]. Our study demonstrated that after adjustment for various confounding factors including FPG and 2hPG, the OR of insulin resistance (IR-Matsuda ISI) and impaired early β -cell response to insulin sensitivity (IB-DI30) remained significant. Interestingly, further adjustment for 2h-PG minished the OR of both IR-Matsuda ISI and IB-DI30, which confirmed the previous study. Further more, the increase of HOMA-IR and decrease of Matsuda ISI of iHH group was lesser than iIFG and iIGT in our study, and the change of DI30 and DI120 in iHH group was also distinguished from iIFG and iIGT. Hence, we deduced that iHH may be another state of dysglycemia, which is distinct from IFG and IGT and indicates different physiopathologic mechanism of hyperglycemia.

A Japanese longitudinal cohort study reported that HbA1c 5.7–6.4% identified fewer individuals at high risk of diabetes than IFG did, however, HbA1c 5.7–6.4% and IFG used together could markedly improve the predictive efficiency for future diabetes [27]. According to these studies and our data, since iHH, IFG and IGT imply distinct pathophysioloic aspects of dysglycemia, the diagnosis for pre-diabetes and diabetes should not rely on only one test of HbA1c, FPG or 2h-PG. Combination of HbA1c and OGTT is necessary for screening and predicting hyperglycemia, this would reduce misdiagnosis at utmost and facilitate the further treatment and prevention of complications.

At present time, the most accurate methods to access insulin sensitivity and β -cell function may be euglycemic-hyperinsulinemic clamp and intravenous glucose tolerance test, which are considered as "gold standard". Because of the large number of studied population in our study, we did not use the clamp and intravenous test. However, we used various kinds of indices to evaluate insulin sensitivity and β-cell function, including HOMA-IR, Matsuda ISI, INSR30, INSR120, DI30 and DI120, which are highly correlated with euglycemichyperinsulinemic clamp and intravenous glucose tolerance test [18]. In addition, this study is cross-sectional, we cannot confirm the causal relationship between iHH and insulin resistance. Nevertheless, subjects with iHH had totally normal FPG and 2h-PG, this may indicate that iHH is another kind of early stage of dysglycemia. Insulin resistance and early-phase β-cell dysfunction in this stage may be a reasonable pathogenic cause, although further prospective study is imperative.

In conclusion, although there was great discordance between HbA1c and blood glucose in the diagnosis of diabetes or prediabetes, HbA1c is not dispensable to identify dysglycemia. iHH is associated with insulin resistance and impaired early-phase β -cell function in middle-aged and elderly Chinese with normal glucose tolerance, which indicated that iHH may be a distinct physiopathologic process of hyperglycemia different from IFG or IGT. Thus, only FPG and 2h-PG is not enough to screen pre-diabetes or newly diagnosed diabetes. Combination of HbA1c and OGTT is recommendable for screening and predicting hyperglycemia.

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Disclosure

No conflicts of interest relevant to this article were reported.

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